REMARKS

Claims 23-27 are pending in this application.

35 U.S.C§ 112

The Examiner has rejected claims 23-27 under 35 U.S.C§ 112 for lack of enabling disclosure. The Examiner has presented the rejections based on 1) the state and unpredictability of the art, 2) the breadth of the claims, and 3) the amount of direction or guidance presented. The Applicant will address each of these points in turn.

The state and unpredictability of the art

The Examiner asserts that the present invention is not enabled because at the time of filing the present application gene therapy was an immature and highly unpredictable art.

As an initial point, Applicant wishes to point out the references cited by the Examiner in the pending Office Action discuss the difficulties associated with the attempt to find **generalized** gene therapy techniques, e.g. to cure genetic diseases etc. Importantly, the Examiner has continued to view the present invention in terms of issues traditionally associated with the term gene therapy, such as vector optimization, optimized quantitative expression of gene product, and prolonged expression of the gene product. Applicant asserts that none of these issues are definitive of the invention as claimed.

By contrast, the invention as claimed is not directed the treatment of genetic defects but rather to methods of treating an ocular wounds by directly contacting an exogenous nucleic acid and an ocular cell *in situ* under conditions permissive for the direct uptake of said exogenous nucleic acid by the ocular cell so that the exogenous nucleic acid is expressed in the ocular cell.

The specification provides sufficient guidance for such methods. The specification teaches the use of a replication-incompetent recombinant adenoviral vector containing a reporter gene, β-galatosidase. The specification also teaches that by directly contacting the adenoviral vector containing the reporter gene with an ocular cell, one can obtain expression

of the reporter gene in the ocular cell. The specification teaches that expression of the reporter gene can be achieved in this manner in both corneal endothelial cells and choroids cells. Thus, the specification provides specific guidance for the type of vector that is useful in the practice of the invention and provides specific guidance for how to directly contact the vector with the ocular cell so as to obtain expression of the gene product.

The fact that the data in the specification shows expression of B-gal and not TGF-beta or other protein that may be used to treat a wound is not an issue because the adenovirus vector can be used to introduce other genes as well. The specification sets forth a delivery system that can be used to introduce any number of genes into ocular cells at a level of efficiency sufficient to result in measurable expression of the introduced gene. Additionally, the specification provides guidance for the introduction of the exogenous nucleic acid into various other ocular cells.

The Examiner's concern regarding the stability of the gene product is misplaced in the context of the present invention. The goal of the invention as presently claimed is to provide treatment for an ocular wound. Thus the goal is to provide expression of the therapeutic gene product to heal an acute injury, not to provide long-term expression of the product. While Applicant asserts that long-term expression of the gene product is enabled by the specification, this issue need not be debated in the context of the present claims.

The Examiner cites the Orkin report for support of assertion regarding the unpredictability of the art. Specifically, the Examiner relies on statements made in page 1-2 of the report wherein the report discusses the general problems surrounding the implementation of gene therapy protocols. As stated above, these problems are directed toward the field of gene therapy as a whole and are not indicative of the enablement of the present invention. As the Orkin report points out on page 1,"many different strategies are being investigated, each with its own set of scientific and clinical challenges", thus recognizing that each individual gene therapy protocol must be analyzed in the context of the problem being addressed and the specific gene therapy-based solution proposed.

Again, the Applicant respectfully refers to an article cited in the response dated March 5, 2001, which describes the successful use of ocular gene therapy. See Bennett et al., *Photoreceptor cell rescue in retinal degeneration (rd) mice by in vivo gene therapy*, Nature Medicine 2(6):649-654 (1996), previously submitted with the response filed October 9, 1999

in the parent case, cited in the IDS filed May 7, 2001 in the present application as reference 24 on form 1449.

Bennett et al. describes the successful gene therapy of rd mice using techniques significantly similar to the techniques outlined in the specification. Bennett et al. use a recombinant adenovirus containing the ßPDE (the rod photoreceptor specific cGMP phosphodiesterase gene), under control of the cytomegalovirus (CMV) promoter. The ßPDE gene replaces the E1 and the majority of the E3 region of a type 5 adenovirus (Ad5). 1×10^8 plaque-forming units (pfu) were injected into the subretinal space of rd mouse eyes. (See page 649, first full paragraph of second column). The presence of the ßPDE gene resulted in the formation of rows of photoreceptor nuclei with delays in photoreceptor cell death, while control mice had virtually no nuclei and significant cell death. The authors conclude that "the findings demonstrate cell rescue by in vivo gene transfer, thus supporting the feasibility of treating an inherited retinal degeneration by somatic gene therapy" (see last sentence of abstract on page 649).

The protocol described in Bennett is very similar to the systems described in the application. Adenoviral vectors are described, both in the examples and on page 14, lines 21-27. In fact, the examples use the CMV promoter as well, in an Ad5 adenovirus which has the CMV/ß- gal construction in place of the E1 region.

Thus, Bennett et al. validates the teachings of the specification, by showing that the specification does indeed provide "therapeutic benefit" .

The Examiner asserts that Bennett is irrelevant to the present application because Bennett describes a subretinal injection of Ad.CMVBPDE at the dosage of $1x10^8$ pfu, conditions not explicitly disclosed in the present specification.

Applicant again submits that Bennett shows that the techniques outlined in the specification are sufficient to enable one skilled in the art to practice the invention as claimed. The specification sets forth that an adenovirus, such as the one exemplified in Bennett, can be used to practice the invention. The specification also provides that conditions permissive for the direct uptake of exogenous nucleic acid by a cell will depend on the form of the exogenous nucleic acid. Thus, for example, when the exogenous nucleic acid is in the form of an adenoviral, retroviral, or adenoassociated viral vector, the permissive conditions are those which allow viral infection of the cell. Specification at page 11, lines 12-16. These

conditions are generally well known in the art and include injection of an adenovirus as set forth in Bennett. Likewise, the concentration of adenovirus to be contacted with the cell could be determined by one of skill in the art without undue experimentation using the guidance of the specification and knowledge of those of skill in the art.

The Examiner also raises concerns that Bennett does not teach wound healing using, for example, TGF-beta. Bennett was cited to rebut the Examiner's broad characterization of the state of the art of gene therapy at the time of filing. Roberts, Massague, Smiddy and Glaser show that TGF-beta could be effectively used to treat ocular wounds.

The breadth of the claims

The Applicant respectfully disagrees with the Examiner that the claims are not enabled for the breadth of their scope. The specification provides sufficient evidence that exogenous nucleic acid can be introduced into and expressed in ocular cells. For example, the exemplified adenovirus vector system used to introduce and express B-Gal in ocular cells can also be used to introduce other nucleic acids for expression in ocular cells. The previously submitted Roberts, Massague, Smiddy and Glaser references show that agents, such as TGF-B, can be introduced into ocular cells to provide a therapeutic effect on ocular wound healing. The Examiner has asserted that the above references cannot be relied on to show the attainment of therapeutic effects in treatment of ocular wounds via gene therapy. These references were not cited for such a purpose but rather to show that feasibility of ocular wound healing. When placed in the context of the present invention, the expression of TGF-beta via an exogenous nucleic acid introduced into an ocular cell would promote wound healing. Again the experimental details surrounding the introduction of an exogenous nucleic acid capable of expressing TGF-beta could be determined by one of skill in the art without undue experimentation using the guidance of the specification and knowledge of those of skill in the art.

Additionally, the specification provides support for the introduction of exogenous nucleic acid into many types of ocular cells including corneal epithelial cells, corneal endothelial cells, cells of the trabecular meshwork, choroids cells, retina, sclera or ciliary body cells, cells of the retinal or ocular vasculature, cells of the vitreous body or cells of the

lens. Specification page 15, line 32, through page 17, line 12. While the specification does not provide examples for each cell type, as discussed above the specification provides the guidance necessary to allow determination of conditions permissive to the uptake of exogenous nucleic acid.

For the reasons set forth above, the invention is enabled for the breadth of the presently pending claims.

The amount of direction and guidance presented

The Examiner has also based the rejection of the claims on the perceived lack of guidance provided by the specification in view of the unpredictability of the art. Applicant believes that the Examiner's concerns in this regard have been addressed in the above arguments. Additionally, as set forth in the prior response, the specification provides a road map for practicing the invention. The Examiner is of the opinion that such a roadmap is not adequate. Applicant respectfully disagrees for the following reasons.

The specification provides the conditions necessary to practice the invention without undue experimentation. For example, conditions used for the cellular uptake of specific forms of exogenous nucleic acids are disclosed. Specification pg. 11, lines 5 –16. The specification directs the use of these general viral techniques when using viral exogenous nucleic acids to facilitate gene therapy of the *in situ* ocular cells. Similarly, the methods of permitting entry of plasmids into a cell were generally known to those of skill in the art and the specification so directs the use of these methods to permit entry of plasmid exogenous nucleic acid to facilitate gene therapy of the *in situ* ocular cells. The specification has further discussions regarding specific conditions for the uptake of various exogenous nucleic acids on page 12, lines 24-31 through page 13, lines 1-3.

The specification further describes conditions permissive for the uptake of the exogenous nucleic acid specific to the cells of the eye. Specification page 12, lines 7-23. The specification states that conditions well known to those of skill in the art that relate to *in vitro* uptake can be applied to *in vivo* ocular cells. The specification then provides specific methods that may be particularly applicable to ocular cells on page 12 lines 13-18.

Furthermore, the specification on page 12, lines 19-23, provides methods of determining when the nucleic acid has been successful taken up by the cell. The Applicant respectfully points out again that under *In re Wands* some experimentation is permissible. The specification provides the direction necessary to guide one of skill in the art to perform the invention with no undue experimentation.

The examples in the specification provide further guidance for determining conditions permissive for the direct uptake of exogenous nucleic acid in ocular cells. Example 1, page 20 lines 1-32, is particularly relevant as this section discusses surgical injury inflicted on a rat's eye and the successful introduction of exogenous nucleic acid into that injury. After direct introduction of the exogenous nucleic acid to the injury, the exogenous nucleic acid was taken up by and expressed protein in the *in situ* ocular cells.

The teachings of the specification provide sufficient guidance for one of skill in the art to practice the invention as claimed.

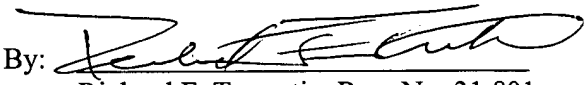
CONCLUSION

The standard for enablement under 35 U.S.C. §112 is that the specification fully enables one skilled in the art to make and use the invention without undue experimentation. For the reasons set forth above, the Applicant submits that the specification, taken in conjunction with the state of the art at the time the invention was filed, (October 31, 1994) fully enabled the skilled artisan to make and use the invention. As such, Applicant respectfully requests withdrawal of the rejections of claims 23-27.

If, upon review, the Examiner feels there are additional outstanding issues which may be resolved by telephone, the Examiner is invited to call the undersigned attorney at (415) 781-1989

Respectfully submitted,

DORSEY & WHITNEY, LLP

By: 
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